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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/447,681	11/23/99	ROTH J	INRP.003--2/

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EXAMINER	
CROUCH, D	
ART UNIT	PAPER NUMBER
1632	12

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Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No.	Applicant(s)	
	09/447,681	ROTH, JACK A.	
	Examiner	Art Unit	
	Deborah Crouch	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Peri d for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *20 February 2001* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *67* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *67* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

11)☒ The proposed drawing correction filed on *11-23-99* is: a)☐ approved b)☒ disapproved.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

15) ☒ Notice of References Cited (PTO-892)
16) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
17) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
18) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
19) ☐ Notice of Informal Patent Application (PTO-152)
20) ☐ Other:

This office action is being remailed to make of record Colicos et al.

Applicant's arguments filed February 20, 2001 in paper no. 10 have been fully considered but they are not persuasive. The amendment has been entered. Claim 67 is pending.

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claim 67 is provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 22,29 and 32-34 of copending Application No. 09/668,532. Although the conflicting claims are not identical, they are not patentably distinct from each other because instant claim 67 is encompasses claims 22,29 and 32-34 of '532. Instant claim 67 is to an adenovirus vector comprising a wild type p53 gene under the control of a CMV promoter. The adenovirus vector of '532 contains an E1 enhancer and an ITR. The adenovirus vector of claim 67 inherently contains the E1 enhancer and ITR. Thus, at the time of the instant invention, the ordinary artisan having claim 67 would have reached the adenovirus of claims 22,29 and 32-34 of '532.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 67 remains rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the

relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention for reasons of record.

There is no disclosure that conveys to the reader that at the time of filing, applicant had possession of an adenovirus vector comprising a wild-type p53 gene under the control of a CMV promoter.

Applicant argues that the specification provides support for claim 67 ins several places. Applicant argues that the specification states that their finding of an increase in transcription rates will be applicable to other promoter/vector constructs at page 8, line 25 to page 9, line 4. Applicant argues that these other vector/promoter constructs are then described through out the specification at page 9, lines 6-12. Applicant argues that the specification contemplates that other vectors can be employed, including adenoviruses at page 14, ,lines 21-23. Applicant argues that the specification states that the promoter is not limited to the β-actin promoter and specifically lists the CMV promoter at page 15, lines 1-4. Applicant argues that the use of adenoviruses in the disclosed at page 14, lines 9-12. Applicant argues that discloses the use of other promoters at page 14, line 35 to page 15, line 2. Applicant argues that the specification clearly states that there is no limitation on the nature of the selected gene to express, and specifically states "sense and antisense" constructs at page 16, lines 5-10. These arguments are not persuasive.

Each of the above citations have been reviewed, and there is no contemplation of the subject matter of claims 67: an adenovirus vector comprising a wild-type p53 gene under the control of a CMV promoter. While there is general language for a contemplation greater than a retrovirus and a β-actin promoter, there is no specific disclosure of another vector construct. The disclosure addresses the broader concept in vague terms with no clear disclosure of claimed invention. Each of applicant's citations provided in the response will be addressed separately.

Page 8, line 25 to page 9, line 4 discusses the discovery that when the selected promoter/gene construct is aligned within the vector in an orientation that is reversed with respect to direction of transcription with respect to other promoters with in the vector, a dramatic increase in transcription of the selected gene is seen. Then the passage goes on to discuss the use of retroviral vectors where the transcription of the selected gene is in reverse orientation to other retroviral transcription. The passage

continues by stating that while the increase in transcription was observed using the β-actin promoter and retroviral vector, the inventors believe that the increase will be seen other promoter/vector constructs. The examiner will agree that applicant has contemplated in general vectors having the gene of interest operatively linked to promoter, and having both in reverse orientation for transcription relative to transcription of other genes in the vector. However, the support for broader than retrovirus does not support the species of adenovirus vector comprising a CMV promoter.

Page 9, lines 6-12 discloses a "specific embodiment" of a vector constructs for introducing wild-type p53 into cells, and states "these embodiments involve the preparation of a gene expression unit where the wt-p53 gene is placed under the control of the β-actin promoter, and the unit is position in a reverse orientation into a retroviral vector." In this discussion, the only contemplation is stated to be a retroviral vector having in reverse orientation a wt-p53 gene operatively linked to a promoter. There is no contemplation of an adenoviral vector comprising a CMV promoter operatively linked to a wt-p53 gene at this place in the specification.

Page 14, lines 21-23 do state that "in addition to retroviruses, it is contemplated that other vectors can be employed, including adenovirus ....". However, if read completely, one would realize that the adenovirus contemplated contains antisense sequences (page 14, lines 9-25). It is clearly stated "although retrovirus would inhibit the growth of the tumor, the expression of the antisense construct in non-tumor cells would be essentially harmless where one prepares a retrovirus construct which encode distinct antisense intron RNA in accordance with the present invention. In addition to retroviruses, it is contemplated that other vectors can be employed, including adenovirus ...". This only support an adenoviral vector comprising an antisense construct and not the adenovirus of claim 67.

Page 15, lines 1-5 states that "while the β-actin promoter is preferred in the invention is by no means limited to this promoter, and one may also mention .....CMV." However, when the entire paragraph is read, "the invention" at this point is the expression of antisense sequences. Please refer to the paragraph at page 14, line 27 "the particular promoter that is employed to control the expression of the antisense RNA in a vector construct is not believed to be particularly crucial ..... where a human cell is

targeted, it will be preferred to position the antisense RNA coding region adjacent to and under the control of a promoter that is capable of being expressed in a human cell ... generally speaking, such a promoter might include either a human cellular or viral promoter..... while the β-actin promoter is preferred .... CMV". A reading of the complete paragraph assigns the citation provided by applicant to refer only to retrovirus vectors expressing antisense. There is no support for claim 67.

Page 14, lines 9-12 state "in broader aspects of the invention, a preferred approach will involve the preparation of retroviral vectors .....", "although the retrovirus would inhibit the growth of the tumor, the expression of the antisense construct in non-tumor cells .....", in addition to retroviruses, it is contemplated .... adenoviruses. As discussed above the entire paragraph, page 14, lines 9-25, contemplates only antisense. There no description of "in broader aspects of the invention" more that expression of antisense sequences in an adenovirus vector. This is not the subject matter of claim 67.

Page 14, line 35 to page 15, line 2, states "generally speaking, such a promoter might include either a human cellular or viral promoter.....". However, when read in the full context, as discussed above (page 14, lines 21-23), the description is for "generally speaking" regarding promoters for use in retroviruses comprising antisense sequences, and not the claimed invention.

Page 16, lines 5-10, state "while the retroviral construct aspect of the present invention concerns the use of a β-actin promoter in reverse orientation, there is no limitation on the nature of the selected gene which one desires to have expressed. Thus the invention concerns the use of antisense-encoding constructs as well as "sense" constructs that encode a desired protein". The specification at this point does not discuss adenovirus as a contemplated vector, the CMV promoter as the contemplated promoter or wt-p53 as the contemplated gene. The passage is confusing as to what other vector aspects there are, and never mentions specifically any other vector construct.

The passages provided by applicant do not provide the type of disclosure that would convey to the artisan that applicant possessed the claimed invention at the time of filing. The are no passages that clearly correlate an adenovirus vector, a CMV promoter and a wt-p53 gene so that the artisan would realize that applicant considered such as part of the invention at the time of filing.

Applicant has provided a declaration by Louis Zumstein, Ph.D. to support their allegations that the specification discloses the subject matter of claim 67. Declarant points to parts of the specification where support can be found. However, these citations, some of which have been discussed above, do not provide the support needed for written description of claim 67, an adenovirus comprising a wt=p53 gene under the control of a CMV promoter.

Page 6, lines 33-35 states "another important oncogene is the gene encoding the p53 cellular protein". The paragraph goes on to discuss the role of p53 mutations in the development of lung cancer. On page 7, line 14, it is stated "one approach that has been suggested as a means of treatment ... is the introduction of so-called 'wild-type' or non-mutated p53 ... through the use of retroviral vectors. A fair reading is the treatment of lung tumors by administering wild-type p53 in a retroviral vector. The passage quoted by declarant, when read in full context, does not provide written description for claim 67.

Page 9, lines 22-23 does not have the stated passage.

Page 15, lines 1-4 has been discussed above (see page 15, lines 1-5).

As the passages cited by declarant do not provide a disclosure that is commensurate with the scope of claim 67, the declaration is not persuasive.

Claims 67 is rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The specification fails to enable the claimed invention as the specification does not provide a source for packaging cell lines for the production of adenoviral vectors that contain the p53 gene in a region of the adenoviral genome essential for replication. It is noted that at the time of filing, 293 cells were known that packaged adenoviral vectors, but only those vectors with a defective E1a region. As for other regions necessary for adenoviral packaging, E2 and E4, the specification nor the art provide a source for packaging cells that complement deletions of this region. Without knowledge of packaging cell lines which complement vectors having E2 and E4 deletions, the bread of the claimed invention is not enabled.

Further, there is also doubt as to the effect of expressing wt-p53 from an adenoviral vector having the E2B gene functional. It is known in the art that E2B proteins binds to the p53 protein and inhibits its activity. Thus, an adenovirus vector producing both p53 and E2B would not be an effective vector. There is no evidence that the CMV promoter would produce sufficient p53 that some portion of the p53 expressed would remain unbound by the E2B protein. This effect would be especially important if the vector were to be used in a therapeutic situation where wild-type p53 was to replace mutant p53. In sufficient wild-type p53 may be left unbound to be effective therapy.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 67 is rejected under 35 U.S.C. 103(a) as being unpatentable over Chen et al (1990) Science 250, 1576-1579 in view of Colicos et al (1991) Carcinogenesis 12, 249-255 further in view of Pasleau et al (1985) Gene 38, 227-232.

Claim 67 is drawn to an adenovirus vector comprising a wild type p53 gene under the control of a CMV promoter.

Chen et al teach retroviral vectors comprising a wild type human p53 operably linked to the retroviral LTR (page 1576, col. 3, Figure 1). Chen et al teach that wild type 53 is expressed in transduced Saos cells, and that the transduced cells failed to form colonies on soft agar or tumors in nude mice (page 1577, col. 2, line 12 to col. 3, line 8). Chen et al also teach that wild type p53 counters the transformation phenotype conferred by a mutant p53 when both genes are present in equal gene dosage (page 1579, col. 1, parag. 1 to col. 2, line 1 and col. 2, parag. 1, lines 25-28). Chen et al do not teach adenoviral vectors comprised of a wild type p53 gene under the control of a CMV promoter. Colicos et al teach the partial complementation of the DNA excision repair function in xeroderma pigmentosa cells comprising infecting the cells in culture with an adenovirus that contains the *denV* gene from bacteriophage T4

operatively linked to an RSV LTR promoter (page 254, col. 1, parag. 2, lines 1-3 and page 249, abstract, lines 8-15). Pasleau teaches a plasmid expression vector comprising a DNA sequence encoding bovine growth hormone, and the production of bGH in transfected rat cells (page 228, col. 2, parag. 1 to page 229, col. 1, line 9 and page 230, col. 2, parag. 1-7). Thus it would have been obvious to the ordinary artisan at the time of the instant invention to prepare an adenoviral vector comprising a human wild type p53 gene operably linked to a CMV promoter as taught by the cited prior art to study mammalian gene expression and the transformed phenotype. Motivation is provided by Chen et al in stating that expression of p53 in Saos cells which lack functional p53 reverts the transformed phenotype (page 1579, col. 1, parag. 1, line 1 to col. 2, line 1). Colicos et al further provides motivation by teaching that adenovirus was selected as it has a broad host range, making it a suitable vector for the study of mammalian gene expression (page 249, col. 2, parag. 3, lines 5-9). Pasleau also offers motivation for the substitution of the CMV promoter for the RSV LTR in stating that the CMV promoter led to the synthesis of three to five times more bGH that the RSV LTR (page 231, col. 1, parag. 1, lines 4-9). All that is required is a reasonable expectation of success in making the claimed vector, and the cited prior art provides such.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Deborah Crouch, Ph.D. whose telephone number is (703) 308-1126.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

The fax number is (703) 308-4242.

Deborah Crouch

DEBORAH CROUCH
PRIMARY EXAMINER
GROUP 1800 1632

Dr. D. Crouch
April 13, 2001